

What is claimed is:

- 10 1. A dosage form of combination of high dose high solubility active ingredient, as modified release and low dose active ingredient as immediate release suitable for swallowing; comprising of dual retard technique to control the release of high dose, high solubility active ingredient, wherein said dosage form comprising of an
15 inner portion having a low dose active ingredient as immediate release and an outer portion having a high dose, high solubility active ingredient as modified release, in which the outer portion comprises a) micro matrix particles and b) coating on micro matrix
20 particles.
2. A dosage form according to claim 1, in the form of a tablet, wherein said inner portion is covered by the outer portion from all the sides except top surface that remains uncovered.
- 25 3. A dosage form according to claim 1, wherein the dosage form is with sufficient reduction in the amount of release controlling agent.
4. A dosage form according to claim 1, wherein the micro matrix particles comprises one or more hydrophobic
30 release controlling agents.
5. A dosage form according to claim 4, wherein the hydrophobic release controlling agents are selected from the group comprising of ammonio methacrylate copolymers type A and B as described in USP, methacrylic acid

5 copolymer type A, B and C as described in USP,
polyacrylate dispersion 30% as described in Ph. Eur.,
polyvinyl acetate dispersion, ethylcellulose, cellulose
acetate, cellulose propionate (lower, medium or higher
molecular weight), cellulose acetate propionate,
10 cellulose acetate butyrate, cellulose acetate phthalate,
cellulose triacetate, poly(methyl methacrylate),
poly(ethyl methacrylate), poly(butyl methacrylate),
poly(isobutyl methacrylate), poly (hexyl methacrylate),
poly(isodecyl methacrylate), poly (lauryl methacrylate),
15 poly(phenyl methacrylate), poly (methyl acrylate), poly
(isopropyl acrylate), poly (isobutyl actylate), poly
(octadecyl acrylate), waxes such as beeswax, carnauba
wax, microcrystalline wax, and ozokerite; fatty alcohols
such as cetostearyl alcohol, stearyl alcohol; cetyl

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alcohol and myristyl alcohol; and fatty acid esters such
as glyceryl monostearate, glycerol distearate, glycerol
monooleate, acetylated monoglycerides, tristearin,
tripalmitin, cetyl esters wax, glyceryl palmitostearate,
25 glyceryl behenate and hydrogenated castor oil.

6. A dosage form according to claim 5, wherein the
hydrophobic release controlling agent(s) is selected
preferably from ammonio methacrylate co-polymers.
7. A dosage form according to claim 6, wherein the preferred
30 ammonio methacrylate co-polymers are selected from
Eudragit RSPO (Ammonio Methacrylate Copolymer type B
USP), Eudragit RL (Ammonio Methacrylate Copolymer type A
USP) and Eudragit NE30D (Polyacrylate dispersion 30% Ph.
Eur.).

5 8. A dosage form according to claim 1, wherein in micro
matrix particles, the active ingredient and one or more
hydrophobic release controlling agents are present in a
ratio of from 100:1 to 100:75.

9. A dosage form according to claim 8, wherein in micro
10 matrix particles, the active ingredient and one or more
hydrophobic release controlling agents are present
preferably in ratio of from 100:2.5 to 100:50.

10. A dosage form according to claim 8, wherein in micro
matrix particles, the active ingredient and one or more
15 hydrophobic release controlling agents are present more
preferably in ratio of from 100:2.5 to 100:30

11. A dosage form according to claim 8, wherein in micro
matrix particles, the active ingredient and one or more
hydrophobic release controlling agents are present most
20 preferably in ratio of from 100:2.5 to 100:20.

12. A dosage form according to claim 1, coating of micro
matrix particles comprises one or more hydrophobic
release controlling agents.

13. A dosage form according to claim 12, wherein the
25 hydrophobic release controlling agents are selected
from the group comprising of ammonio methacrylate
copolymers type A and B as described in USP, methacrylic
acid copolymer type A, B and C as described in USP,
polyacrylate dispersion 30% as described in Ph. Eur.,
30 polyvinyl acetate dispersion, ethylcellulose, cellulose
acetate, cellulose propionate (lower, medium or higher
molecular weight), cellulose acetate propionate,
cellulose acetate butyrate, cellulose acetate phthalate,
cellulose triacetate, poly(methyl methacrylate),

5 poly(ethyl methacrylate), poly(butyl methacrylate),
poly(isobutyl methacrylate), poly (hexyl methacrylate),
poly(isodecyl methacrylate), poly (lauryl methacrylate),
poly(phenyl methacrylate), poly (methyl acrylate), poly
(isopropyl acrylate), poly (isobutyl actylate), poly
10 (octadecyl acrylate), waxes such as beeswax, carnauba
wax, microcrystalline wax, and ozokerite; fatty alcohols
such as cetostearyl alcohol, stearyl alcohol; cetyl
alcohol and myristyl alcohol; and fatty acid esters such
as glyceryl monostearate, glycerol distearate, glycerol
15 monooleate, acetylated monoglycerides, tristearin,
tripalmitin, cetyl esters wax, glyceryl palmitostearate,
glyceryl behenate glycerol distearate, and hydrogenated
castor oil.

14.A dosage form according to claim 13, wherein the
20 hydrophobic release controlling agent(s) is selected
from fatty acid esters.

15.A dosage form according to claim 14, wherein the
hydrophobic release controlling agents is selected from
the group comprising of hydrogenated castor oil and
25 glycerol distearate.

16.A dosage form according to claim 1, wherein in outer
portion, micro matrix particles and coating of one or
more hydrophobic release controlling agents are present
in a ratio of from 100:0.5 to 100:75.

30 17.A dosage form according to claim 16, wherein in outer
portion, micro matrix particles and coating of one or
more hydrophobic release controlling agents are present
preferably in a ratio of from 100:1 to 100:50.

- 5 18.A dosage form according to claim 16, wherein in outer
portion, micro matrix particles and coating of one or
more hydrophobic release controlling agents are more
preferably present in a ratio of from 100:2.5 to 100:20.
- 10 19.A dosage form according to claim 1, wherein the weight
ratio of immediate release active ingredient and
modified release active ingredient is from 1:10 to
1:15000.
- 15 20.A dosage form according to claim 1, wherein the low dose
active ingredient comprises dose less than or equal to
50 mg.
- 20 21.A dosage form according to claim 1, wherein the low
dose active ingredient is selected from the group
comprising of antidiabetic agents, anti-histamines,
anti-depressants, anti-viral agents, anesthetics,
antacids, anti-arththriics, antibiotics, anti-
psychotics, anti-spasmodics, anxiolytic agents, appetite
suppressants, cardiovascular agents, cough suppressants,
emollients, gastro-intestinal agents, growth regulators,
respiratory stimulants, vitamins, angiotensin converting
25 enzyme inhibitors, anti-asthmatics, anti-
cholesterolemics, anti-convulsants, anti-depressants,
anti-diarrhea preparations, anti-infective, anti-
inflammatory agents, anti-nauseants, anti-stroke agents,
anti-tumor drugs, anti-tussives, anti-uricemic drugs,
30 amino-acid preparations, antiemetics, antiobesity drugs,
antiparasitics, antipyretics, appetite stimulants,
cerebral dilators, chelating agents, cholecystokinin
antagonists, cognition activators, deodorants,
dermatological agents, diuretics, erythropoietic drugs,
35 fertility agents, synthetic hormones, laxatives, mineral

5 supplements, neuroleptics, neuromuscular agents,
peripheral vaso-dilators, prostaglandins, vaginal
preparations, vaso-constrictors, vertigo agents,
sulphonylurease, meglitinides, PPAR gama agonist
[insulin sensitisers (thiazolidinedione)], PPAR alpha
10 and gamma agonist, alpha-glucosidase inhibitors and the
like.

22.A dosage form according to claim 21, wherein the low
dose active ingredient is selected from the group
comprising of zafirlukast, quinapril hydrochloride,
15 isotretinoin, rabeprazole sodium, estradiol(e2),
norethindrone acetate, risedronate sodium, pioglitazone
HCl, amphetamine, anagrelide hydrochloride, biperiden
HCl, mephalan, alprazolam, ramipril, naratriptan
hydrochloride, leflunomide, anastrozole, exemestane,
20 paroxetine mesylate, candesartan cilexetil, almotriptan,
cerivastatin, betaxolol hydrochloride, bisoprolol
fumarate, deloratadine, clonazepam, clorazepate
dipotassium, clozapine, methylphenidate hci, carvedilol,
warfarin sodium, norgestrel, ethinyl estradiol,
25 cyclophosphamide, pemoline, liothyronine sodium,
misoprostol, tolterodine tartrate, dextroamphetamine
sulfate, dicyclomine hydrochloride, digoxin, oxybutynin
chloride, doxazosin mesylate, ethacrynate sodium,
venlafaxine HCl, enalapril maleate, estradiol,
30 estropipate, famotidine, letrozole, fludrocortisone
acetate, fluoxetine, dexmethylphenidate hci, alendronate
sodium, ziprasidone, glipizide, glyburide, miglitol,
guanabenz acetate, haloperidol, doxercalciferol,
zalcitabine, hydrochlorothiazide, hydromorphone HCl,
35 indapamide, estradiol, nitric oxide, ketorolac

5 tromethamine, clonazepam, granisetron, lamotrigine,
 fluvastatin sodium, levonorgestrel, levothyroxine
 sodium, atorvastatin calcium, lisinopril, minoxidil,
 loperamide, loratidine, lorazepam, lovastatin,
 pravastatin sodium, fluvoxamine maleate, acetaminophen,
 10 acyclovir, aminocaproic acid, pitavastatin,
 rosuvastatin, dalvastatin, escitalopram, sertraline, celecox
 ib, parecoxib, valdecoxib, glibenclamide
 (glyburide), glipizide, gliclazide, glimepiride,
 tolazamide, tolbutamide, clorpropamide, gliquidone,
 15 nateglinide, glyburide, glisoxepid, glibornuride,
 phenbutamide, tolcyclamide, repaglinide, troglitazone,
 ciglitazone, pioglitazone, englitazone, acarbose,
 voglibose, emiglitate, miglitol, farglitazar, (S)-2-
 ethoxy-3-[4-(2-(4-
 20 methanesulfonyloxyphenyl)ethoxy)phenyl]propanoic acid,
 3-[4-[2-(4- tert-butoxycarbonylaminophenyl)
 ethoxy]phenyl]-(S)-2-ethoxy propanoic acid, L-6766892
 and pharmaceutically acceptable salts thereof.

23. A dosage form according to claim 1, wherein the high
 25 dose, high solubility active ingredient comprises dose
 from 500 mg to 1500 mg.

24. A dosage form according to claim 1, wherein the high
 dose, high solubility active ingredient is selected from
 the group comprising of antidiabetic agents, anti-
 30 histamines, anti-depressants, anti-viral agents,
 anesthetics, antacids, anti-arthritis, antibiotics,
 anti-psychotics, anti-spasmodics, anxiolytic agents,
 appetite suppressants, cardiovascular agents, cough
 suppressants, emollients, gastro-intestinal agents,
 35 growth regulators, respiratory stimulants, vitamins,

5 angiotensin converting enzyme inhibitors, anti-
asthmatics, anti-cholesterolemics, anti-convulsants,
anti-depressants, anti-diarrhea preparations, anti-
infective, anti-inflammatory agents, anti-nauseants,
anti-stroke agents, anti-tumor drugs, anti-tussives,
10 anti-uricemic drugs, amino-acid preparations,
antiemetics, antiobesity drugs, antiparasitics,
antipyretics, appetite stimulants, cerebral dilators,
chelating agents, cholecystokinin antagonists, cognition
activators, deodorants, dermatological agents,
15 diuretics, erythropoietic drugs, fertility agents,
synthetic hormones, laxatives, mineral supplements,
neuroleptics, neuromuscular agents, peripheral vaso-
dilators, prostaglandins, vaginal preparations, vaso-
constrictors, biguanides, vertigo agents and the like.

20 25. A dosage form according to claim 1, wherein the high
dose, high solubility active ingredient is selected from
the group comprising of metformin hydrochloride,
phenformin, buformin, potassium chloride, clindamycin,
hydroxyurea, erythromycin, lactobionate, vancomycin
25 hydrochloride, balsalazide disodium, sodium valproate,
niacin, aminocaproic acid, acetaminophen ciprofloxacin,
quetiapine and pharmaceutically acceptable salts
thereof.

30 26. A dosage form according to claim 1, wherein inner
portion may optionally contain more than one low dose
active ingredients.

35 27. A dosage form according to claim 1, wherein the
dissolution of high dose, high solubility active
ingredient is not more than 45% in 1 hour and between
25% to 90% in 6 hours.

- 5 28. A dosage form according to claim 1, wherein the dosage form can be given twice a day or more preferably can be given once a day oral formulation.
29. A dosage form according to claim 1, is used for human beings.
- 10 30. A process for the preparation of a dosage form comprising a) preparation of inner portion and b) preparation of outer portion.
31. A process for the preparation of a dosage form as claimed in claim 30, wherein preparation of outer
15 portion comprising a) preparing a micro matrix particles containing high dose, high solubility active ingredient and one or more hydrophobic release controlling agent and b) coating the said micro matrix particles containing high solubility active ingredient and one or
20 more hydrophobic release controlling agent.
32. A dosage form according to claim 1, wherein outer portion may optionally contain more than one high dose high solubility active ingredients.
33. A dosage form of combination of high dose high
25 solubility antidiabetic active ingredient is as modified release and low dose antidiabetic active ingredient as immediate release, suitable for swallowing; comprising of dual retard technique to control the release of the high dose high solubility antidiabetic active ingredient
30 wherein said dosage form comprising of an inner portion having a low dose antidiabetic active ingredient as immediate release and an outer portion having a high dose high solubility antidiabetic active ingredient as modified release, in which the outer portion comprises

5 a) micro matrix particles and b) coating on micro matrix particles.

34. A dosage form according to claim 33, which is a tablet, in which the inner portion is covered by the outer portion from all the sides except top surface that
10 remains uncovered.

35. A dosage form according to claim 33, wherein the dosage form is with sufficient reduction in the amount of release controlling agent.

36. A dosage form according to claim 33, wherein the micro
15 matrix particles comprises one or more hydrophobic release controlling agents.

37. A dosage form according to claim 36, wherein the hydrophobic release controlling agents are selected from the group comprising of ammonio methacrylate copolymers
20 type A and B as described in USP, methacrylic acid copolymer type A, B and C as described in USP, polyacrylate dispersion 30% as described in Ph. Eur., polyvinyl acetate dispersion, ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher
25 molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly (hexyl methacrylate),
30 poly(isodecyl methacrylate), poly (lauryl methacrylate), poly(phenyl methacrylate), poly (methyl acrylate), poly (isopropyl acrylate), poly (isobutyl actylate), poly (octadecyl acrylate), waxes such as beeswax, carnauba wax, microcrystalline wax, and ozokerite; fatty alcohols

5 such as cetostearyl alcohol, stearyl alcohol; cetyl
alcohol and myristyl alcohol; and fatty acid esters such
as glyceryl monostearate; glycerol monooleate,
acetylated monoglycerides, tristearin, tripalmitin,
cetyl esters wax, glyceryl palmitostearate, glyceryl
10 behenate, glycerol distearate and hydrogenated castor
oil.

38.A dosage form according to claim 37, wherein the
hydrophobic release controlling agent(s) is selected
preferably from ammonio methacrylate co-polymers.

15 39. A dosage form according to claim 38, wherein the
preferred ammonio methacrylate co-polymers are selected
from Eudragit RSPO (Ammonio Methacrylate Copolymer type
B USP), Eudragit RL (Ammonio Methacrylate Copolymer type
A USP) and Eudragit NE30D (Polyacrylate dispersion 30%
20 Ph. Eur.).

40. A dosage form according to claim 33, wherein in micro
matrix particles, the antidiabetic active ingredient and
one or more hydrophobic release controlling agents are
present in a ratio of from 100:1 to 100:75.

25 41. A dosage form according to claim 40, wherein in micro
matrix particles, the antidiabetic active ingredient and
one or more hydrophobic release controlling agents are
present preferably in ratio of from 100:2.5 to 100:50.

42. A dosage form according to claim 40, wherein in micro
30 matrix particles, the antidiabetic active ingredient and
one or more hydrophobic release controlling agents are
present more preferably in ratio of from 100:2.5 to
100:30

5 43. A dosage form according to claim 40, wherein in micro matrix particles, the antidiabetic active ingredient and one or more hydrophobic release controlling agents are present most preferably in ratio of from 100:2.5 to 100:20.

10 44. A dosage form according to claim 33, wherein coating of micro matrix particles comprises one or more hydrophobic release controlling agents.

45. A dosage form according to claim 44, wherein the hydrophobic release controlling agents are selected from
15 the group comprising of ammonio methacrylate copolymers type A and B as described in USP, methacrylic acid copolymer type A, B and C as described in USP, polyacrylate dispersion 30% as described in Ph. Eur., polyvinyl acetate dispersion, ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher
20 molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly (hexyl methacrylate),
25 poly(isodecyl methacrylate), poly (lauryl methacrylate), poly(phenyl methacrylate), poly (methyl acrylate), poly (isopropyl acrylate), poly (isobutyl actylate), poly (octadecyl acrylate), waxes such as beeswax, carnauba wax, microcrystalline wax, and ozokerite; fatty alcohols
30 such as cetostearyl alcohol, stearyl alcohol; cetyl alcohol and myristyl alcohol; and fatty acid esters such as glyceryl monostearate; glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin,
35 cetyl esters wax, glyceryl palmitostearate, glyceryl

5 behenate, glycerol distearate and hydrogenated castor oil.

46. A dosage form according to claim 45, wherein the hydrophobic release controlling agent(s) is selected from fatty acid esters.

10 47. A dosage form according to claim 46, wherein the hydrophobic release controlling agents are selected from the group comprising of hydrogenated castor oil and glycerol distearate.

15 48. A dosage form according to claim 33, wherein in outer portion, micro matrix particles and coating of one or more hydrophobic release controlling agents are present in a ratio of from 100:0.5 to 100:75.

20 49. A dosage form according to claim 48, wherein in outer portion, micro matrix particles and coating of one or more hydrophobic release controlling agents are present preferably in a ratio of from 100:1 to 100:50.

25 50. A dosage form according to claim 48, wherein in outer portion, micro matrix particles and coating of one or more hydrophobic release controlling agents are more preferably present in a ratio of from 100:2.5 to 100:20.

51. A dosage form according to claim 33, wherein the weight ratio of immediate release antidiabetic active ingredient and modified release antidiabetic active ingredient is from 1:10 to 1:15000

30 52. A dosage form according to claim 33, wherein the low dose antidiabetic active ingredient comprises dose less than or equal to 50 mg.

- 5 53. A dosage form according to claim 33, wherein the low dose
antidiabetic active ingredient is selected from the
group comprising of sulphonylurease, meglitinides, PPAR
gamma agonist [insulin sensitisers (thiazolidinedione)],
10 alpha-glucosidase inhibitors, PPAR alpha and gamma
agonist.
54. A dosage form according to claim 33, wherein the low
dose antidiabetic active ingredient is selected from the
group comprising of glibenclamide (glyburide), glipizide,
gliclazide, glimepiride, tolazamide, tolbutamide,
15 clorpropamide, gliquidone, nateglinide, glyburide,
glisoxepid, glibornuride, phenbutamide, tolcyclamide,
repaglinide, troglitazone, ciglitazone, pioglitazone,
englitazone, acarbose, voglibose, emiglitate, miglitol,
farglitazar, (S)-2-ethoxy-3-[4-(2-{4-
20 methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid,
3-{4-[2-(4- tert-butoxycarbonylaminophenyl)
ethoxy]phenyl}-(S)-2-ethoxy propanoic acid and
pharmaceutically acceptable salts thereof.
55. A dosage form according to claim 33, wherein the high
25 dose high solubility antidiabetic active ingredient is
selected from biguanides.
56. A dosage form according to claim 33, wherein the high
dose high solubility antidiabetic active ingredient is
selected from the group comprising of metformin
30 hydrochloride, phenformin and buformin
57. A dosage form according to claim 33, wherein the high
dose high solubility antidiabetic active ingredient
comprises dose from 500 mg to 1500 mg.

5 58. A dosage form according to claim 33, is once a day oral formulation.

59. A dosage form according to claim 33, is used for human beings.

10 60. A dosage form according to claim 33, wherein the high dose high solubility antidiabetic active ingredient is metformin hydrochloride.

15 61. A dosage form according to claim 33, wherein the composition of outer portion is as follows-

Micro matrix particles-

Metformin hydrochloride	75%w/w to 99%w/w
Eudragit RS	1%w/w to 25%w/w

20 Coated micro matrix particles

Micro matrix particles	70%w/w to 99%w/w
Hydrogenated castor oil	1%w/w to 30%w/w
Magnesium stearate	0%w/w to 2%w/w

25 62. A dosage form according to claim 33, wherein the dissolution of metformin hydrochloride is not more than 50% in one hour, from 30 to 90 % in four hours and not less than 65 % in twelve hours.

30 63. A dosage form according to claim 33, wherein the maximum plasma metformin concentration is achieved between 700 ng/ml and 2500 ng/ml.

5 64. A dosage form according to claim 63, wherein the maximum plasma metformin concentration is achieved preferably between 900 ng/ml and 2400 ng/ml.

65. A dosage form according to claim 63, wherein the maximum
10 plasma metformin concentration is achieved more preferably between 1000 ng/ml and 2350 ng/ml.

66. A dosage form according to claim 33, wherein the modified release metformin hydrochloride formulations
15 for once daily administration exhibit invivo mean dissolution time (MDT) of 4 hours to 6 hours.

67. A dosage form according to claim 33, wherein the minimum plasma metformin concentration (at 24 hours) ranges
20 between 0 and 450 ng/ml after oral administration.

68. A dosage form according to claim 33, wherein the low dose antidiabetic active ingredient is rosiglitazone maleate.

25 69. A dosage form according to claim 33, wherein the low dose antidiabetic active ingredient is glimepiride.

70. A dosage form as claimed in claim 60 and 68, wherein the
30 bioavailability of rosiglitazone is not affected when it is coadministered with metformin hydrochloride.

71. A dosage form according to claim 33, wherein inner portion may optionally contain more than one antidiabetic active ingredients.

5 72.A dosage form according to claim 33, wherein outer
portion may optionally contain more than one
antidiabetic active ingredients.

73.A process for the preparation of a dosage form as
claimed in claim 33, comprising a) preparation of inner
10 portion and b) preparation of outer portion.

74. A process for the preparation of a dosage form as
claimed in claim 73, wherein preparation of outer
portion comprising a) preparing a micro matrix particles
containing high dose, antidiabetic active ingredient and
15 one or more hydrophobic release controlling agent and
b) coating the said micro matrix particles containing
high dose antidiabetic active ingredient and one or more
hydrophobic release controlling agent.

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